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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/720,431	11/24/2003	Takuji Shirasawa	2352.001	5106
23405	7590	11/14/2006	EXAMINER	
HESLIN ROTHENBERG FARLEY & MESITI PC 5 COLUMBIA CIRCLE ALBANY, NY 12203			HIRIYANNA, KELAGINAMANE T	
			ART UNIT	PAPER NUMBER
			1633	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/720,431

Applicant(s)

SHIRASAWA ET AL.

Examiner

Kelaginamane T. Hiriyanne

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response filed on 8/22/2006 in response to office action mailed on 03/22/2006 has been acknowledged.

Claims 1 and 12-13 are cancelled

Claims 7 is amended

Claims 2-11 *are pending and are examined in this office action. Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

(I). Objections to specification and denial of priority is removed in view of applicants inclusion of a copy of the foreign priority document and the amendment to specification to include a cross reference to related application

(II). Objection to claim 7 is removed in view of applicants' corrections to the cited claims.

(III). Rejection of claims 1 and 12 under 102(b) as being anticipated by Hoffman et al., (Patent No. US 5,028,588) is withdrawn in view of applicants cancellation of cited claims.

(IV). Rejection of claims 5-10 under 35 USC 103 (a) as being unpatentable over Hoffman et al., (Patent No. US 5,028,588) in view of Li et al (2000, Nature Medicine 6:1115-1120) is hereby withdrawn in view of new art rejections encompassing the cited claims.

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(V). Rejection of claim 11 under 35 USC 103 (a) is hereby withdrawn in view of new rejection below.

(VI). Rejection of claims 2-4 under 35 USC 103 (a) as being unpatentable over Hoffman et al., (Patent No. US 5,028,588) and Standl et al (2001, Expert. Opin. Biol. Ther. 1:831-843) and in view of Baron et al (1999, Critical Care 3:R99-R102) is hereby withdrawn in view of new art rejections encompassing the cited claims.

Response to Arguments (8/22/2006)

The applicant argues that since cancellation of claims 1 and 12 Hoffmans reference is not applicable as in combination with Snadl's or Baron's references. Applicant further argues that he discusses "superior effect of the alleviation of tissue hypoxia" and Hoffman does not mention the potential superiority of the Titusville mutant over other mutation and Sandl et al casually mentions recombinant hemoglobin.

However this is found not persuasive. Hoffmans reference also teaches a method of use of hemoglobin with Titusville mutation for supplementing the oxygen carrying capacity of blood as further detailed below. Hence it is applicable as a reference as previously cited with modifications indicated in rejection of claims under 35 USC102 as above. Further the applicants arguments above are not found persuasive since they do not specifically address or reflect the scope of the instant claims.

Claim Rejections - 35 USC § 102

(VII). Claims 2-10 are rejected under 102(b) as being anticipated by Hoffman et al., (Patent No.US 5,028,588).

The above claims are directed to a method of alleviating hypoxia, preventing ischemic condition, enhancing oxygen metabolism, enhancing exercise capacity and modifying a tissue, comprising treating a subject with α -globin having the Titusville mutation.

Regarding claims 2-10 Hoffman teaches a method of treating a patient (subject) in need of tissue oxygenation with Titusville mutant hemoglobins that are useful as substitutes for red blood cells in delivery of oxygen to tissues (see col.27-28, claims 1-2, 22). With reduced affinity for oxygen (low oxygen affinity state; 'right-shifted') for efficient

unloading of bound oxygen in tissues in need of O₂ (e.g., ischemic condition), a limitation observed with native hemoglobin, when used as a blood substitute (col. 1-2). Hoffman further teaches that one can use either certain naturally occurring mutants in α or β chain of the hemoglobin or use non-naturally occurring low affinity hemoglobin mutants (col.3-5, col.21-22 and table 1; col.24, Table 2, col.27-28). He further points out specifically the use of a Titusville mutant where in Asp94Asn of α -globin (col.28, claim 22) as one of the preferred candidates. Preferential use of the hemoglobin mutants with P₅₀ at least 10% higher than conventional hemoglobin is to supplement the oxygen carrying-capacity of patients blood (col.27, 2nd paragraph) and further it is implicit from the prior art that the use of such mutant hemoglobins having lower oxygen affinity is to alleviate hypoxia under any conditions it occurs (including due to ischemic conditions and it is inherent that oxygen enhances metabolism in tissues, modifies tissues and enhances exercise capacity of a treated individual). Thus the rejected claims are within the scope of the Hoffman's, disclosure.

(VIII). Claim 11 is rejected under 35 USC 103 (a) as being unpatentable over Hoffman et al., (Patent No. US 5,028,588) as applied to claim 2-10 above in view of Abraham et al (Patent No. US 5,661,182) and further in view of De la Torre (Ann N Y Acad Sci.2002 Nov; 977:196-215).

The above claims are directed to a method for treating or preventing cerebrovascular dementia comprising treating a subject with α -globin having the Titusville mutation.

Regarding claims 2-10 Hoffman teaches a method of treating a patient (subject) in need of tissue oxygenation with Titusville mutant hemoglobins that are useful as substitutes for red blood cells in delivery of oxygen to tissues (see col.27-28, claims 1-2, 22). With reduced affinity for oxygen (low oxygen affinity state; 'right-shifted') for efficient unloading of bound oxygen in tissues in need of O₂ (e.g., ischemic condition), a limitation observed with native hemoglobin, when used as a blood substitute (col. 1-2). Hoffman further teaches that one can use either certain naturally occurring mutants in α or β chain of the hemoglobin or use non-naturally occurring low affinity hemoglobin mutants (col.3-

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5, col.21-22 and table 1; col24, Table 2, col.27-28). He further points out specifically the use of a Titusville mutant where in Asp94Asn of α -globin (col.28, claim 22) as one of the preferred candidates. Preferential use of the hemoglobin mutants with P_{50} at least 10% higher than conventional hemoglobin is to supplement the oxygen carrying-capacity of patients blood (col.27, 2nd paragraph) and further it is implicit from the prior art that the use of such mutant hemoglobins having lower oxygen affinity is to alleviate hypoxia under any conditions it occurs (including due to ischemic conditions and it is inherent that oxygen enhances metabolism in tissues, modifies tissues and enhances exercise capacity of a treated individual). However, Hoffman does not teach treating or preventing cerebrovascular dementia with mutant hemoglobin.

Abraham teaches the use of low oxygen affinity hemoglobin as a blood substitute to treat ischemia, heart disease, wound healing, some forms of Alzheimers (a form of cerebrovascular vascular dementia), depression, schizophrenia, adult respiratory distress syndrome etc." (Abstract and col.2, lines 33-43) that may be caused by low oxygen supply. Abraham further teaches allosterically modifying hemoglobin towards a low oxygen affinity state in whole blood using modifying drug compounds. This is equivalent to modifying hemoglobin with tiutsville mutation that brings down the affinity of hemoglobin for oxygen.

De la Torre teaches that there is now substantial evidence that sporadic alzheimers disease is a disorder of vascular disorder or vascular dementia (p.196, abstract). De la Torre provides epidemiologic evidence linking vascular factors for cerebrovascular pathology that can set in motion metabolic, neurodegenerative and cognitive changes in Alzheimers brain (p.197, 3rd & last paragraphs).

Thus it would have been obvious for one of ordinary skill in the art to use Titusville mutant hemoglobin as with low oxygen affinity state as a blood substitute as taught by Hoffman and contemplate a method of treating conditions such as cerebro-vascular dementia a form of Alzheimers disease/cerebrovascular dementia as taught by Abraham. One of ordinary skill in the art would have been motivated to employ the erythrocyte free hemoglobin compositions with Titusville mutation in alpha subunit, as it lowers oxygen affinity of hemoglobin and enhances tissue oxygenation, and may preventing or treat

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vascular dementia or Alzheimers. One of ordinary skill in the art would have reasonable expectation of success in making and using blood transfusion substitutes hemoglobin with Titusville mutation and treat of vascular dementia because of the teachings in the art as above. Thus, the claimed invention is *prima facie* obvious.

Response to Arguments (8/22/2006)

The applicant argues that Hoffman combined with Abrahams and De La Torres references are not appropriate because Abraham only teaches a hemoglobin which is allosterically modified to reduce the oxygen affinity and De la Torre only mentions vascular disease but does not mention blood.

However this is found not persuasive. Hoffmans reference clearly teaches the use of hemoglobin with Titusville mutation for supplementing the oxygen carrying capacity of blood because its oxygen affinity is lowered and hence able to supply oxygen to tissues more efficiently to tissues. Abrahams' allosteric modification of hemoglobin is done with the same intention to lower the oxygen affinity of hemoglobin and to use it as a more efficient blood substitute to supply oxygen to hypoxic tissues. Further the purpose of using the mutant blood with Titusville mutation or Abraham modified blood is same. Hence it is clearly applicable as a reference as previously cited. Further De la Torre is one of the first one to show alzheimers is a vascular dementia. A vascular disease always inherently refers to a status of altered blood supply. Thus it is clearly applicable as a supporting reference here.

Conclusion:

No claim allowed.

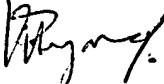
Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hirianna* whose telephone number is (571) 272-3307. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is 571 272-0548. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at (571) 272-0731. The fax phone number for the organization where this application or


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proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

Kelaginamane T. Hiriyanne

Patent Examiner

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SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER